Phosphodiesterase Type 5 Inhibitors

A phosphodiesterase type 5 inhibitor (PDE5 inhibitor) is a drug used to block the degradative action of cGMP-specific phosphodiesterase type 5 (PDE5) on cyclic GMP in the smooth muscle cells lining the blood vessels supplying various tissues.

These drugs dilate the corpora cavernosa of the penis, facilitating erection with sexual stimulation, and are used in the treatment of erectile dysfunction (ED). Sildenafil was the first effective oral treatment available for ED. Because PDE5 is also present in the smooth muscle of the walls of the arterioles within the lungs, sildenafil and tadalafil dilates those vessels, and are FDA-approved for the treatment of pulmonary hypertension.

Medical uses

PDE5 inhibitors such as sildenafil (Viagra), tadalafil (Cialis), and vardenafil (Levitra) are clinically indicated for the treatment of erectile dysfunction.

Sildenafil and tadalafil are also indicated for the treatment of pulmonary hypertension.

Sildenafil, the prototypical PDE5 inhibitor, was originally discovered during the search of a novel treatment for angina. Studies in 2002 explored its potential for increasing neurogenesis after stroke.

Contraindications

PDE5 inhibitors are contraindicated in those taking nitrate medications, such as isosorbide mononitrate or isosorbide dinitrate.

Concurrent use of these medications can lead to life-threatening low blood pressure or heart attack.

They are also contraindicated in men for whom sexual intercourse is inadvisable due to cardiovascular risk factors.

Adverse effects

The occurrence of adverse drug reactions (ADRs) with PDE5 inhibitors appears to be dose-related. Headache is a very common ADR, occurring in >10% of patients. Other common ADRs include: dizziness, flushing, dyspepsia, nasal congestion or rhinitis.

In 2007, the U.S. Food and Drug Administration (FDA) announced that a warning about possible sudden hearing loss would be added to drug labels of PDE5 inhibitors.

Since 2007 there is evidence that PDE5 inhibitors can cause an anterior optic neuropathy.

Other ADRs and their incidence vary with the agent and are listed in their individual pages.

Drug interactions

PDE5 inhibitors are primarily metabolized by the cytochrome P450 enzyme CYP3A4. The potential exists for adverse drug interactions with other drugs which inhibit or induce CYP3A4, including HIV protease inhibitors, ketoconazole, and itraconazole.

Combination with nitrovasodilators such as nitroglycerin and PETN is contraindicated because potentially life-threatening hypotension may occur.

Examples

Sildenafil was the prototypical member of the PDE5 inhibitors. Many other agents, both natural and synthetic, are available, including:

1- Avanafil

2- Lodenafil

3- Mirodenafil

4- Sildenafil

5- Tadalafil

6- Vardenafil

7- Udenafil

8- Zaprinast

9- Benzamidenafil

10- Dasantafil

While these drugs preferentially inhibit PDE5, none of them are truly selective, especially at high doses. Sildenafil also inhibits PDE6 and PDE9, with inhibition of PDE6 in the retina thought to be responsible for the vision changes which can be a side effect of the drug. Similarly tadalafil inhibits both PDE5 and PDE11.

However the selectivity of the existing drugs is high enough that inhibition of additional PDE subtypes is not generally a problem in clinical use, and while newer "super-selective" PDE5 inhibitors[specify] have been developed for research purposes, it is unlikely any of these will be marketed given the saturation of the erectile dysfunction market at present. Nevertheless PDE5 inhibitors are important for far more effects than merely erectile dysfunction.

Caffeine is a non-selective PDE inhibitor, and inhibits PDE5 at well under toxic dosages.

Mechanism of action

Part of the physiological process of erection involves the release of nitric oxide (NO) in vasculature of the corpus cavernosum as a result of sexual stimulation. NO activates the enzyme guanylate cyclase which results in increased levels of cyclic guanosine monophosphate (cGMP), leading to smooth muscle relaxation in blood vessels supplying the corpus cavernosum, resulting in increased blood flow and an erection.

PDE5 inhibitors inhibit the degradation of cGMP by PDE5, increasing bloodflow to the penis during sexual stimulation. This mode of action means that PDE5 inhibitors are ineffective without sexual stimulation.